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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/684,109	10/10/2003	Peter J. DeVries	6989.US.02	5090

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EXAMINER	
XIE, XIAOZHEN	
ART UNIT	PAPER NUMBER
1646	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/07/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/684,109	DEVRIES ET AL.	
	Examiner	Art Unit	
	Xiaozhen Xie	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-60* is/are pending in the application.

4a) Of the above claim(s) *6-8,14-35,38,39,42-45,47,48 and 55-59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,9-13,36,37,40,41,46,49-54 and 60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20040901,20050914,20060515*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

The Information Disclosure Statement (IDS) filed 1 September 2004, 14 September 2005, and 15 May 2006 has been entered.

Applicant's election without traverse of Group I, claims 1-41, 46, 49-54 and 60, and species: A) SEQ ID NO: 3; B) SEQ ID NO: 5; C) SEQ ID NOs: 51 and 53; D) SEQ ID NO: 58; E) SEQ ID NO: 62; H) Ab12, in the reply filed on 4 December 2006 is acknowledged. Claims 1-60 are pending. Claims 42-45, 47, 48 and 55-59 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 1-41, 46, 49-54 and 60 are under examination. Claims 1-5, 9-13, 36, 37, 40, 41, 46, 49-54, and 60 read on elected species.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-5, 9-11, 49, 52 and 53 are rejected under 35 U.S.C. 101 because the claims are directed to non-statutory subject matter. Because they do not require that the antibody be isolated, they encompass products of nature, which are not patentable. This rejection could be overcome by addition of the limitation wherein the antibody is isolated.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 9, 10, 12, 13, 36, 37, 40, 41, 46, 49-54 and 60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

1) an isolated antibody or antibody fragment thereof, that is capable of binding to a human EpoR and activates an endogenous activity of the EpoR in a mammal, comprising at least one heavy chain variable region having the amino acid sequence of SEQ ID NO: 3 and at least one light chain variable region having the amino acid sequence of SEQ ID NO: 5;

2) an isolated antibody or antibody fragment thereof, that is capable of binding to a human EpoR and activates an endogenous activity of the EpoR in a mammal, comprising at least one heavy chain variable region having the amino acid sequence of SEQ ID NO: 51 and at least one light chain variable region having the amino acid sequence of SEQ ID NO: 53;

3) an isolated antibody capable of binding to a human EpoR in a mammal, comprising a heavy chain variable region comprising a continuous sequence from CDR1 through CDR3 having the amino acid sequence of SEQ ID NO: 58 and a light chain variable region comprising a continuous sequence from CDR1 through CDR3 having the amino acid sequence of SEQ ID NO: 62;

does not reasonably provide enablement for the genus of the antibodies or antibody fragment thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

The instant claims are broad in that they encompass a genus, i.e.,

1) antibodies or antibody fragments thereof that activate an endogenous activity of the EpoR in a mammal wherein the antibodies or antibody fragments thereof do not interact with a peptide having an amino acid sequence of SEQ ID NO: 1 (claims 1), or exhibits a binding affinity <100-fold compared to endogenous EPO/EpoR, (claim 2), or are gamma-2 isotype (claims 49-54);

2) the antibodies of 1) comprise at least one heavy chain variable region or at least one light chain variable region (claims 3, 4, 9, 10);

3) antibodies or antibody fragments thereof that are capable of binding to a human EpoR in a mammal, wherein the antibodies comprise at least one heavy chain variable region or at least one light chain variable region (claims 12, 13, 36, 37, 40, 41);

4) a pharmaceutical composition comprising an antibody or antibody fragment thereof that does not interact with a peptide having an amino acid sequence of SEQ ID NO: 1, or that activates an endogenous activity of the EpoR in a mammal (claims 46, 60).

The specification discloses the isolated monoclonal or humanized antibodies that are capable of binding to a human EpoR and activates an endogenous activity of the EpoR in a mammal, such antibodies comprise a heavy chain variable region and a light chain variable region having the amino acid sequence of SEQ ID NO: 3/SEQ ID NO: 5, respectively, or SEQ ID NO: 51/SEQ ID NO: 53, respectively, or SEQ ID NO: 58/SEQ ID NO: 62, respectively. The specification, however, does not provide sufficient guidance for making the genus of EpoR binding or activating antibodies that possess the same properties. There is no teaching in the specification as to what structural characteristics are necessary and sufficient for the functionality of the molecule, or what changes could be made without loss of function. While the prior art teaches the same antibodies, it fails to provide compensatory guidance. Further, it is well known in the art that even minor changes in sequence can result in major changes in function, especially if the minor sequence change occurs within an active site or alters the overall

conformation of the molecule. For example, Cacia et al. (Biochemidtry, 1996, Vol. 35, pp. 1897-1903) teach the effect on antigen binding of an isomerized Asp residue located in the CDRs of a recombinant monoclonal antibody. Cacia et al. found that changing Asp-L32 decreased the relative binding affinity for IgE significantly (pp. 1901, see section "Interaction of E25 variants with IgE", and Table 4). Similarly, Rudikoff et al. (Proc. Natl. Acad. Sci, USA, 1982, Vol. 79:1979-1983) teach that the alteration of a single amino acid in the CDR of an antibody resulted in the loss of antigen-binding function. In addition, the claims read on antibodies or antibody fragments that require only heavy chain variable region or light chain variable region structure defined. Alberts et al. teach that the antigen-binding domain is made up of the light chain and heavy chain variable regions (The Cell, 2002, Garland Science, 4th edition, esp. pp. 161, Fig. 3-42). Similarly, do Couto et al. teach that both the light chain and heavy chain variable regions are generally required for the binding properties of an antibody (U.S. Patent NO: 6,309,636B1, see column 7, lines 32-34). Therefore, without detailed guidance in the specification regarding the structures or data supporting the claims drawn to the genus of the antibody, one of ordinary skill in the art would not know how to use the invention commensurate in scope with the claims.

Due to the large quantity of experimentation necessary to generate the nearly infinite number of human EpoR activating or binding antibodies and antibody fragments thereof recited in the claims, and screen same for the binding specificity and functional activities, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide the binding specificity and functional

activities, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on antibody function, the breadth of the claims which fail to recite any structural limitations for the antibody, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim 54 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention appears to employ novel biological materials, specifically the antibody or antibody fragment Ab12. Since the biological materials are essential to the claimed invention they must be obtainable by a repeatable method set forth in the specification or otherwise readily available to the public. If the biological materials are not so obtainable or available, the requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the biological materials. The specification does not disclose a repeatable process to obtain the biological materials and it is not apparent if the biological materials are readily available to the public. It is noted that Applicant has deposited the biological materials (p. 34-35 of the specification), but there is no indication in the specification as to public availability. Also the claim only provides the name "Ab12" which is not defined and no structure is provided. It is suggested to placing in brackets next to "Ab12" the actual deposit number. If the deposit is made under the Budapest Treaty, then an

affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific biological materials have been deposited under the Budapest Treaty and that the biological materials will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, and that the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer, would satisfy the deposit requirement made herein. If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 C.F.R. §§ 1.801-1.809, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer;

(d) a test of the viability of the biological material at the time of deposit will be made (see 37 C.F.R. § 1.807); and

(e) the deposit will be replaced if it should ever become inviable.

Applicant's attention is directed to M.P.E.P. §2400 in general, and specifically to §2411.05, as well as to 37 C.F.R. § 1.809(d), wherein it is set forth that "the

specification shall contain the accession number for the deposit, the date of the deposit, the name and address of the depository, and a description of the deposited material sufficient to specifically identify it and to permit examination." The specification should be amended to include this information, however, Applicant is cautioned to avoid the entry of new matter into the specification by adding any other information. Finally, Applicant is advised that the address for the ATCC has recently changed, and that the new address should appear in the specification. The new address is:

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10801 University Boulevard

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Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 3-5, 9-13, 36, 37 and 54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is indefinite for reciting "wherein said antibody or antibody fragment thereof exhibits a binding affinity within one hundred fold of the binding affinity of endogenous human erythropoietin to the erythropoietin receptor". The claim is directed to an antibody or antibody fragment thereof that is capable activating an endogenous activity of a human EpoR, and the claim does not define the binding partner. Therefor, it is unclear what binding affinity the claim is referred to. The artisan would not be able to

compare a binding affinity for the antibody or antibody fragment thereof to that of endogenous human erythropoietin to the erythropoietin receptor.

Claims 3-5, 9-13, 36 and 37 are indefinite in the recitation of "at least one heavy (or light chain) variable region having the amino acid sequence of SEQ ID NO: X or antibody fragment thereof". Heavy chain and light chain are subunits of an antibody. It is not clear what fragment the claims are intended to encompass.

Claim 54 is rejected as vague and indefinite for reciting the term Ab12 as the sole means of identifying the claimed molecule. The use of laboratory designations only to identify a particular molecule renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct molecules. "Ab12" is not defined and no structure is provided. One skilled in the art cannot determine the metes and bounds of the term without structure.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 46, 49-54 and 60 are rejected under 35 U.S.C. 102(b) as being anticipated by Elliott et al. (U. S. Patent No: 5,885,574, issued on Mar. 23, 1999).

Elliott teaches an antibody, Mab 73, which activates a human EpoR and stimulates the proliferation of UT7-EPO cells (Fig. 2, and figure legend in column 4,

lines 36-38) (claim 1). Elliott teaches that Mab 73 has no effect on inhibition of EPO binding to EPO receptors on the surface of OCIM1 cells (Fig. 3, and figure legend in column 4, lines 39-42), suggesting that Mab 73 does not interact with a peptide of SEQ ID NO: 1, because the amino acid sequence of SEQ ID NO: 1 corresponds to amino acid residues 74-103 of human EpoR precursor, and the extracellular domain of EpoR spans between amino acid residues 52-250 (see alignment) (claims 1 and 53). Elliott teaches that the antibody exhibits a binding affinity within 100-fold of the binding of Epo-EpoR (Fig. 3) (claim 2). Elliott also teaches that the antibody can be monoclonal antibody, humanized antibody, or human antibody (column 4, lines 22-23) (claims 50-52 and 54). Elliott further teaches the antibody can be used in a pharmaceutical composition for treating disorders characterized by low red blood cell levels in a mammal (column 7, lines 21-51) (claims 46 and 60). Although Elliott is silent regarding the limitation of a gamma-2 isotype (claim 49), it is one of the known inherent properties of human IgGs. Therefore, the '574 patent anticipates claims 1, 2, 46, 49-54 and 60.

Conclusion

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Xiaozhen Xie, Ph.D whose telephone number is 571-272-5569. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol, Ph. D. can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Xiaozhen Xie, Ph. D.
January 26, 2007

Michael D. Pak
MICHAEL PAK
PRIMARY EXAMINER